REMARKS

I. Status of the Claims

Claims 1-3, and 8-10 are currently under examination on their merits.

II. Claim Rejections Under 35 U.S.C. §102(b)

Claims 1-3, and 8 stand rejected under 35 U.S.C. §102(b) in view of U.S. Patent No. 5,723,313 by Sherr et al. (hereinafter "Sherr"). In response to Applicants' argument filed on February 13, 2007, the Office issued an Advisory Action maintaining the rejection. The Action asserts that Sherr contemplates fragments of the full length p19ARF. The Action further alleges that Sherr teaches "introducing" p19ARF protein into mammalian cells, which the Action interprets to encompass "contacting" the cell with a p19ARF protein. Applicants respectfully traverse.

The claimed invention is directed to a method of inhibiting proliferation of a tumor cell comprising the step of contacting the cell with a p19ARF protein *fragment* having the amino acid sequence of SEQ ID NO:10. Sherr merely relates to the effect of p19ARF *full length* protein on cell cycle regulation. Both the American Heritage Dictionary and Stedman Medical Dictionary defines a "fragment' as "a small part broken off or detached" and "n incomplete or isolated portion; a bit." A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. M.P.E.P. 2131. *citing Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Applicants submit that the Sherr reference does not anticipate their pending claims, because it does not teach a fragment of is not an anticipatory reference because it does not teach a fragment and thus does not each and every element of the claim. Moreover, the Sherr reference does not teach the specific fragment (SEQ ID NO: 10) that is recited as an affirmative limitation to their pending claims. Applicants this respectfully contend that the asserted reference does not fulfill the requirements of M.P.E.P 2131 as an anticipating reference, and request that the Examiner withdraw this ground of rejection.

1. Sherr does not teach a method of inhibiting tumor cell proliferation with a p19ARF protein fragment having the amino acid sequence of SEQ ID NO:10

As the asserted basis for the §102 rejection, the Action relies on Sherr's sweeping disclosure of "synthetic oligopeptides that generally contain from about 5 to about 100

contiguous amino acids" of p19ARF protein. *See* Sherr, column 16, line 57 to column 17, line 3, and page 2 of the Advisory Action. The disclosure teaches, if anything, nothing other than an extremely broad genus of p19ARF protein fragments. Applicants submit that the broad genus does not teach or suggest the claimed p19ARF protein fragment having the amino acid sequence of SEQ ID NO:10.

In a genus-species situation, a genus does not anticipate a species within the genus, *unless* the species is clearly named. MPEP §2131.02. If the species is not clearly named, anticipation can only be found if the classes of substitution are sufficiently limited or well delineated. *Id.* Alternatively, "[i]f one of ordinary skill in the art is able to 'at once envisage' the specific compound within the generic chemical formula, the compound is anticipated." *Id.* One of skill in the art must be able to readily pinpoint the species within the broad genus before any species can be "at once envisaged."

Applicants submit that the §102 rejection over Sherr is improper because the broad genus of p19ARF protein fragments does not anticipate the specifically claimed species. Sherr's broad genus encompasses a plethora of protein fragments. Sherr does not provide any guidance in selecting a fragment among all potential "oligopeptides that generally contain from about 5 to about 100 contiguous amino acids." The broad genus is not sufficiently limited and is poorly-delineated. Sherr does not identify, with any particularity, the claimed species fragment having the amino acid sequence of SEQ ID NO:10. One of ordinary skill in the art will not be able to readily pinpoint the claimed species fragment from Sherr's broad genus, nor does the Action provide any reasoning arguing otherwise (because there isn't any). Thus, Sherr cannot and does not anticipate the claimed invention because Sherr does not teach or suggest the claimed p19ARF protein fragment.

2. Sherr does not teach a method of inhibiting tumor cell proliferation by <u>contacting</u> the tumor cell with a p19ARF protein fragment having the amino acid sequence identified in SEQ ID NO:10.

Applicants remind the Office that the pending claims are *method* claims, and an anticipatory reference must teach every step of the claimed method. Sherr does not teach or suggest a method of inhibiting cell proliferation comprising a step of "contacting" a tumor cell with a p19ARF protein fragment; rather, the reference teaches a method in which the full length protein is "expressed" in the tumor cell.

In response to Applicants' argument, the Action cites Sherr's disclosure of "introduced into mammalian cells ARF-p19 proteins" in column 16, lines 53-56. The Action asserts that "introducing ARF-p19 into the cell is interpreted as encompassing contacting the cell with a p19ARF protein fragment." See page 2 of the Advisory Action. However, this is nothing more than hindsight reconstruction of the Sherr teachings. The Action fails to point to a single portion or citation in the reference that would support such an interpretation. Throughout the disclosure of Sherr, the phrase "introduced into mammalian cells ARF-p19 protein" refers *only* to delivering an exogenous genetic material, such as DNA, into cells by transfection, retroviral infection, or transgenic techniques, and expressing p19ARF protein in the cell from the genetic material. Sherr does not provide any example of, or even mention, contacting the cell with any p19ARF protein fragment. There is no evidence that Sherr contemplates inhibiting tumor cell growth by contacting the cell with a p19ARF protein fragment. Indeed, if any employee of the Patent and Trademark Office is aware of any reference or citation that would have taught the person of ordinary skill in the art that p19ARF could be "delivered" into a cell by merely contacting the cell with the protein, Applicants invite the Office to supply such information pursuant to the provisions of 37 C.F.R. §1.104(d)(2).

Additionally, Applicants submit that Sherr is not an anticipatory reference because it does not enable one of skill in the art to inhibit tumor cell proliferation by contacting the cell with any p19ARF protein fragment, let alone the claimed p19ARF fragment. In order to qualify as anticipatory prior art, the reference must contain "an enabling disclosure." *In re Hoeksema*, 399 F.2d 269 (CCPA 1968). The disclosure in a purported anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or describing subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003).

In this case, Sherr does not provide any example in which cells were contacted with any p19ARF protein fragment, let alone the claimed fragments, and into which the fragment was thus "delivered." Moreover, Sherr does not teach that a protein fragment can be delivered into a cell by merely contacting the fragment with the cell. Nor does Sherr show that any protein fragment that might be taken up by the cells in this manner could inhibit cell proliferation. And Sherr does not teach *which* protein fragment might inhibit cell proliferation, if it were to be delivered. One of ordinary skill in the art would not be able to practice the claimed invention based on Sherr

without undue experimentation. Thus, Sherr does not anticipate the claimed subject matter because it does not enable the claim limitation.

Applicants respectfully reiterate that in order to anticipate, a cited reference must encompass each and every limitation of the putatively-anticipated claims. Here, Sherr fails to teach, *inter alia*, the claimed p19ARF protein fragments, and inhibiting proliferation of a tumor cell by contacting the cell with the claimed protein fragments. Accordingly, Applicants respectfully request withdrawal of rejection under 35 U.S.C. §102(b).

III. Claim Rejections Under 35 U.S.C. §103(a)

Claims 1 and 9-10 stand rejected in the Final Office Action under 35 U.S.C. 103(a) as being unpatentable over Sherr in view of Laes et al. (*Cancer Genet Cytogenet* 117:118-124, 2000) (hereinafter "Laes") The Advisory Action maintains the rejection and asserts that Sherr contemplates p19ARF protein fragments. The Action further asserts that the teaching of introducing p19ARF protein into cells in Sherr encompasses the claimed method of contacting a p19ARF fragment with the cells. Applicants respectfully traverse the rejection.

The Supreme Court in Graham set out the factual inquiry, which the Patent Office must follow in determining obviousness. *Graham v John Deere Co.*, 383 U.S. 1, 17 (1966). The inquiry includes (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating evidence of secondary considerations. When applying §103 as set forth in *Graham v John Deere*, the following tenets of patent law must be adhered to:

(a) the claimed invention must be considered as a whole;

(b) the reference must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(c) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(d) reasonable expectation of success is the standard with which obviousness is determined.

MPEP §2141 *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1986). Further, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP §2143.03 (*citing In re Royka*, 490 F.2d 981 (CCPA 1974)). It is incumbent upon the Office to come forward with articulated reasoning with

some rational underpinning to support the legal conclusion of obviousness. *KSR Int'l v. Teleflex, Inc.*, No. 04-1350, slip op. at 14 (2007). *citing In re Kahn*, 441 F.3d 977 (Fed. Cir. 2006). Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness over Sherr in view of Laes.

The claims of the instant invention are directed to a method of inhibiting tumor cell growth comprising a step of inhibiting FoxM1B activity by contacting the cell with a p19ARF protein fragment having the amino acid sequence of SEQ ID NO:10. As set forth in Part II above, Sherr merely relates to the effect on cell cycle regulation of expressing full-length p19ARF. Sherr's overly broad genus of p19ARF protein fragments does not teach the particular fragments having the sequence of SEQ ID NO: 10. Based on Sherr, none of the most frequently mutated residues in the Ink4A/p19ARF region in cancers falls within the sequence of SEQ ID NO: 10. For example, residues Gly-68, Pro-93, Arg-97, and Arg-114 all fall outside amino acid residues 26-44. *See* Sherr, col. 34, lines 56-62. Thus, not only would it not have been obvious to one skilled artisan to choose a fragment having the amino acid sequence identified by SEQ ID NO: 10, but the Sherr reference teaches away from amino acid residues 26-44 for inhibiting tumor cell growth by pointing the skilled artisan to an amino acid sequence comprising amino acids from Gly-68 through Arg-114. Additionally, Sherr only teaches recombinant expression of the full-length p19ARF protein inside a cell from exogenous DNA molecules. Such a recombinant expression method differs completely from the claimed method in which the cell takes up the protein fragment by contacting the fragments with the cell. Indeed, the present invention could not be more different from the combination of the cited references.

The deficiencies are not cured by Laes. Laes merely showed that in rodent hepatoma cells the p19ARF RNA is either absent or is expressed as a mutated form. In one mouse hepatoma cell line analyzed, the mutation would potentially encode a truncated p19ARF protein. The putative truncated p19ARF protein would retain *only* the N-terminal 15 amino acids of the wild type p19ARF. *See* Laes, Figure 2. This sequence is not part of and is not identified by SEQ ID NO: 10. Of the remaining portion of the sequence, Laes does not teach or suggest which *portion* of all the missing amino acid residues (residues 16-169) is important in inhibiting tumor growth. More particularly, Laes does not teach or suggest that the claimed p19ARF protein fragment having amino acid residues 26-44 inhibits tumor growth. In fact, Laes does not teach or suggest whether a p19ARF protein fragment, instead of the full length protein, can inhibit

tumor cell proliferation. Further, Laes does not teach or suggest a method of inhibiting tumor cell growth by merely contacting the cell with any p19ARF protein fragment.

The Action does not provide any articulated reasoning (and in fact, no reasoning whatsoever) as to why one of ordinary skill in the art would have combined Sherr with Laes, and more importantly, why the combination would allegedly lead to the claimed invention. The cited art, either alone or in combination, does not teach or suggest the desirability of the claimed invention. The combination does not logically lead to the selection of a p19ARF fragment having the sequence of SEQ ID NO:10. Similarly, the method does not logically lead to a method in which the protein fragment is not *expressed* inside the cell; but rather, the fragment is taken up by the cell by *contacting* the cell with the fragment. Further, the Action failed to establish a *prima facie* case of obviousness because the combination does not teach or suggest every element of the claims. Thus, Applicants submit that it would not have been obvious to a skilled artisan the method of inhibiting tumor cell proliferation by contacting the cell with a p19ARF protein fragment having amino acid sequence of SEQ ID NO:10 with a reasonable expectation of success over cited art.

Additionally, neither Sherr et al, nor Laes et al., alone or in combination, teaches or suggests a method of inhibiting tumor cell growth comprising a step of inhibiting FoxM1B activity by the p19ARF peptide having the sequence of SEQ ID NO:10. It was the Applicants' unexpected discovery that the p19ARF peptide inhibits FoxM1B activity. For example, Applicants unexpectedly discovered that p19ARF binds FoxM1B protein. See Example 15. Applicants also discovered that the p19ARF 26-44 sequence alone is sufficient to bind and inhibit FoxM1B transcriptional activity. See Example 18. Applicants further discovered that the p19ARF 26-44 peptide inhibits FoxM1B protein by sequestering FoxM1B in nucleolus. See Example 19. Additionally, Applicants disclosed that the p19ARF 26-44 peptide reduces FoxM1B-induced colony formation on soft agar. See Example 20. Nowhere in the prior art, and certainly in neither Sherr nor Laes, was there any teaching or suggestion of the role of FoxM1B in tumor cell growth. Neither reference teaches or suggests the effect of *any* p19ARF protein fragment, much less the *particular* protein fragment as set forth in SEQ ID NO:10, on the transcriptional activity of FoxM1B.

Thus, claims 1, and 9-10 would not have been obvious to one skilled in the art in view of Sherr and Laes, alone or in combination. Consequently, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

IV. Conclusions

Applicants respectfully submit that all conditions of patentability are met in the pending claims. Allowance of the claims is thereby respectfully solicited.

Once the claims are found allowable, Applicants respectfully request the Office reinstate and allow the non-elected species SEQ ID NOs: 11 and 12, in the form of Examiner's Amendment. MPEP §809.02(a).

The Examiner in charge of this application is invited to contact the undersigned representative at the telephone number set forth below if it is believed to be helpful.

Respectfully submitted,

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